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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
09/729,264	11/28/00	WELCHER A	A-692

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HM12/0717

EXAMINER	
WHITEMAN, B	
ART UNIT	**PAPER NUMBER**
1633	8

DATE MAILED: 07/17/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary	Application No. 09/729,264	Applicant(s) WELCHER ET AL.	
	Examiner Brian Whiteman	Art Unit 1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-56* is/are pending in the application.

4a) Of the above claim(s) *9,12-45,49-54 and 56* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10,11,46-48 and 55* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *2* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Priority

Priority to an U.S. provisional application 60/214,512 filed 28 June 2000 is acknowledged.

Information Disclosure Statement

The information disclosure statement filed on 28 November 2000 does not fully comply with the requirements of 37 CFR 1.98 because: applicant does not properly cite the journal article(s) listed on the 1449. The title of each journal article is missing on pages 1, 2, and 3 of the IDS. The date of BH is incorrect and should read June 6, 1985. Several articles provide a table of context but no relevant pages (DL, DM, EA, and EL). Foreign patents labeled BF and BG are in German and the examiner does not read or speak German.

The examiner has considered all references except for BF, BH, BG, DL, DM, EA, and EL. In order to have all of the references initialed and dated on the 1449, an English translation of the German patents (BF and BG); relevant pages of each journal article (DL, DM, EA, and EL); and a new 1449 properly citing the articles must be filed with the response to this office action. Failure to comply with this notice will result in the above mentioned information disclosure statement being placed in the application file with the non-complying information not being considered. See 37 CFR 1.97(i).

Applicant's election with traverse of Group I, claims 1-8, 10, 11, 46-48, and 55, in paper no. 7 is acknowledged. The traversal is on the ground(s) that: 1) The examiner has not established that there is an undue burden in searching sequences SEQ ID NOs: 1, 3, and 5. 2) The amino acid sequences encoded by SEQ ID NOs 1, 3, and 5 share a sequence identity of greater than 99% (exhibit A, page 3).

In conclusion, the applicants' traversal with respect to issues 1 and 2, listed above, are found persuasive and SEQ ID NOs: 1, 3, and 5 will be examined in this instant application.

Claims 9, 12-45, 49-54 and 56 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, there being no allowable generic or linking claim. In addition, SEQ ID NOs 7-14 are withdrawn from further consideration by the examiner. Election was made with traverse in Paper No. 7.

Elected claims 1-8, 10, 11, 46-48, and 55 with respect to SEQ ID NOs 1-6, to which the following grounds of rejection are applicable, are pending examination.

Claims 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 46-48, and 55 are objected to as being improper dependent because the claim is dependent on a non-elected claim(s). Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claims 1, 2, 3, 4, 5, 6, 7, 8, 10, 11, 46-48, and 55 should be amended to reflect the elected invention of Group I. Should applicant amend the claims, so that the claims no longer resemble the elected invention, another restriction may be necessary.

The as-filed specification is objected to because of the following informalities:

On page 106, there is a space between intracerebral and (intra-parenchymal) line 6.

Clarification is requested.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Claims 1-8, 10, 11, 46-48, 55, as best understood, are rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably provide enablement for the presently pending claims encompassing any isolated polynucleotides or polypeptide sequence encoding a B-7 like molecule. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The claimed invention is an isolated polynucleotide sequence (SEQ ID NOs 1, 3, or 5) encoding a B-7 like molecule and the amino acid sequences encoding a B-7 like molecule (SEQ ID NOs 2, 4, or 6). In addition, the claimed invention uses the nucleic acid molecule of claim 1, 2, or 3 in a method of modulating levels of a polypeptide in an animal. Furthermore, the applicants claim a pharmaceutical composition comprising a nucleic acid of claims 1, 2, or 3, wherein the nucleic acid is contained in a viral vector. The disclosure also claims a viral vector comprising a nucleic acid of claims 1, 2, or 3. In view of the elected invention lies in the field of gene therapy.

At the time the application was filed the state of the art for gene therapy as exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that

factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

The as-filed specification contemplates several methods of gene therapy using the polypeptides and polynucleotides of the claimed invention. In addition, it is not apparent to one skilled in the art what biological properties consist of a B7-like molecule. The prior art recites that B-7, expressed on antigen presenting cells, provides a crucial co-stimulatory signal for T cell activation (Freeman et al., *J. Exp. Med.*, Vol. 178, 1993, pp. 2185-2191). It is not apparent from the disclosure how the SEQ ID NOs: 1-6 are related to B-7 or a B7 like molecule. Furthermore, the claimed invention does not specify what polypeptide in an animal would be modulated when the nucleic acid molecule encoding SEQ ID NOs: 1, 2, 3, 4, 5, or 6 is administered. The as-filed specification does not provide sufficient guidance for how modulating levels of a polypeptide in an animal comprising administering to the animal the nucleic acid molecule of SEQ ID NOs: 1-6 correlates to a therapeutic effect in any animal. In view of the state of the art as exemplified by Anderson and Verma regarding gene therapy, it would take one skilled in the art an undue amount of experimentation to determine how to use the nucleic acid sequences (SEQ ID NOs: 1, 3, or 5) and/or the nucleic acid sequences encoding the polypeptide sequences (SEQ ID NOs; 2, 4, or 6) in any method of gene therapy for any disease.

Furthermore, the as-filed specification encompasses determining the percent identity of the isolated nucleic acid molecule according to claim 2 using a computer program selected from GAP, BLASTP, BLASTN, FASTA, BLASTA, BLASTX, BestFit, and the Smith-Waterman

algorithm. The disclosure also claims nucleotide sequences, which hybridizes under moderately or highly stringent conditions to the complement of SEQ ID NOs 1-6 and a nucleotide sequence complementary to any nucleotide sequence encoding SEQ ID NOs: 1-6. In addition, the specification contemplates claims directed to a nucleotide sequence encoding a polypeptide that has a substitution and/or deletion of 1 to 100 amino acid residues as set forth in SEQ ID NOs: 1, 3, or 5, wherein the encoded polypeptide has an activity of the mature form of a polypeptide as set forth in SEQ ID NOs: 2, 4, or 6. In view of the state of the art and the as-filed specification, it is apparent that one skilled in the art would be able to determine the percent identity of SEQ ID NOs: 1-6. However, it is not apparent to one skilled in the art if the nucleic acid sequences with a substitution and/or deletion of 1 to 100 amino acid residues or nucleotide sequence which hybridizes under moderate condition to the complement of SEQ ID NOs: 1, 3, 5 have B7 or B7 like activity. In addition, it not apparent to one skilled in the art how the nucleic acid sequences complementary to any nucleotide sequence encoding SEQ ID NOs: 1-6 exhibit biological activity as contemplated by the specification. Since, the relationship between a sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable (e.g. see Chiu et al., *Folding and Design*, 1998, pp. 23-228), it would required undue experimentation for one skilled in the art to arrive at other peptides that have B7 or B7 like activity. In addition, in *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.,* 18 USPQ2d 1016 (Fed. Cir. 1991), the court ruled that a claim to a large genus of possible genetic sequences encoding a protein with a particular function that needs to be determined subsequent to the construction of the genetic sequences may not find sufficient support under 35 U.S.C. 112, first paragraph, if only a few of the sequences that meet the functional limitations of the claim are disclosed and if

undue experimentation would be required of one skilled in the art for the determination of other genetic sequences that are embraced by the claim. This is the case here. In other words, since it would require undue experimentation to identify other peptides that have B7 or B7 like activity, it certainty would require undue experimentation to make their corresponding DNA and, therefore, the entire scope of claims 1-3 and 11 are not enabled.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made do not enable one skilled in the art to use the claimed invention. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any animal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to how the biological function of any of the DNA molecules encoding a sequence (SEQ ID NOs 1-6) cited in the claims corresponds to a therapeutic effect in any animal, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 2, 3, 8, 10, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The phrase "moderately or highly stringent conditions" in claim 1-3 is a relative phrase, which renders the claim indefinite. The phrase "moderately or highly stringent conditions" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite

degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The definition of the phrase "moderately or highly stringent conditions" is not a closed definition from reading pages 27-30 in the as-filed specification. The parameters of what constitutes moderately or highly stringent conditions are not defined by the claims.

The term "B7-like polypeptide" in claims 8 and 10 is a relative term, which renders the claim indefinite. The term "B7-like polypeptide" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The metes and bounds of a B7-like polypeptide are not defined by the specification

Claim 47 recites the limitation "A composition of claim 46" in lines 24, page 159. There is insufficient antecedent basis for this limitation in the claim. It is not apparent as to what a composition is referring to as defined in claims 46.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3, as best understood are readable to the extent on any nucleotide sequence complementary to a nucleotide sequence that hybridizes under moderately or stringent conditions encoding a fragment of two or more nucleotide base pairs from a nucleotide sequence encoding SEQ ID NOs: 1-6 [*e.g.* claim 1g(e)].

Claims 1-3 are rejected under 35 U.S.C. 102(a) as being anticipated by Marra et al (The Washington University-NCI Mouse EST project, seq_name: gb_est82: BF040046, July 2, 1999).

Marra discloses an est sequence with 85 percent similarity that would hybridizes under moderate conditions encoding a nucleotide sequence from SEQ ID NO: 1-6.

No claims are allowed

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Ms. Tracey Johnson whose telephone number is (703) 305-2982.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775. The examiner can normally be reached on M-F, (730-400 EST).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Deborah Clark can be reached at (703) 305-4051.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 746-5024.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1633
July 13, 2001

DAVE T. NGUYEN
PRIMARY EXAMINER